CALCIUM BLOCKERS TO TREAT PROLIFERATIVE RETINAL DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation-in-part of U.S. Patent Application Serial No. 10/436,902, filed on May 12, 2003, which is a continuation of U.S. Patent Application Serial No. 10/038,215, filed on January 2, 2002, which is a continuation of U.S. Patent Application Serial No. 09/445,832 which was filed on December 13, 1999 as the U.S. National Patent Application of PCT/US98/12414, which was filed on June 15, 1998 and was based on U.S. Provisional Application 60/051,962, which was filed on June 30, 1997 in the name of Dreyer for CALCIUM BLOCKERS TO TREAT PROLIFERATIVE VITREORETINOPATHY. All of the aforementioned patent applications are expressly incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates to the treatment of diseases related to the proliferation or migration of retinal pigment epithelium and/or glial cells.

BACKGROUND OF THE INVENTION

Many diseases or conditions which threaten a person's vision are believed to be related to the migration or proliferation of retinal pigment epithelium and/or glial cells. Some examples of such diseases are non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, acute macular neuroretinopathy, cystoid macular edema, diabetic macular edema, Behcet's disease, diabetic retinopathy, retinal arterial occlusive disease, central retinal vein occlusion, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser treatment, conditions caused by photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal membranes, proliferative diabetic retinopathy,

branch retinal vein occlusion, anterior ischemic optic neuropathy, non-retinopathy diabetic retinal dysfunction, and retinitis pigmentosa.

BRIEF DESCRIPTION OF THE INVENTION

We have discovered that glutamate causes migration and proliferation of retinal pigment epithelium and/or glial cells. The use of glutamate antagonists to reduce or control retinal pigment epithelium and/or glial migration and the subsequent development of diseases or conditions is disclosed herein. Disclosed herein is a method of treating a disease or condition wherein migration or proliferation of retinal pigment epithelium or glial cells causes or contributes to the cause of said disease or condition, comprising administering a therapeutically effective amount of a compound which is a glutamate agonist to the patient suffering from said disease or condition.

DETAILED DESCRIPTION OF THE INVENTION

In relation to the methods of treating disclosed herein, the disease or condition being treated is a disease or condition wherein migration or proliferation of retinal pigment epithelium or glial cells causes or contributes to the cause of said disease or condition. The relationship may be direct or indirect, and the migration or proliferation retinal pigment epithelium or glial cells may be a root cause of said disease or condition, or may be a symptom of another underlying disease or condition. While not intending to limit the scope of the invention in any way, the following are examples of the types of diseases or conditions treated by the disclosed method: non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, acute macular neuroretinopathy, cystoid macular edema, diabetic macular edema, Behcet's disease, diabetic retinopathy, retinal arterial occlusive disease, central retinal vein occlusion, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser treatment, conditions caused by photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal

membranes, proliferative diabetic retinopathy, branch retinal vein occlusion, anterior ischemic optic neuropathy, non-retinopathy diabetic retinal dysfunction, and retinitis pigmentosa.

In one method, disease or condition is selected from the group consisting of non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, acute macular neuroretinopathy, cystoid macular edema, diabetic macular edema, Behcet's disease, diabetic retinopathy, retinal arterial occlusive disease, central retinal vein occlusion, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser treatment, conditions caused by photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal membranes, branch retinal vein occlusion, anterior ischemic optic neuropathy, non-retinopathy diabetic retinal dysfunction, and retinitis pigmentosa.

In another embodiment the disease or condition is not proliferative vitreoretinopathy.

In another method, the disease is proliferative diabetic retinopathy.

While not desiring to be bound to any specific theory, we conclude that one or more of the several types of calcium-permeable CNS ion channels mentioned below can be involved in controlling such migration, including: a) the various aspects of the NMDA (N-methyl-D-aspartate) receptor channel complex; b) the voltage-dependent Ca.sup.2+ channels; and c) other channels directly coupled to glutamate (or excitatory amino acid) receptors. Such channels are reviewed in: Sommer, B. and Seeburg, P. H. "Glutamate receptor channels: novel properties and new clones" Trends Pharmacological Sciences 13:291-296 (1992); Nakanishi, S., "Molecular Diversity of glutamate receptors and implications for brain function", Science 248:597-603 (1992).

The compound may be one of the so-called NMDA antagonists--i.e., it reduces neuronal damage mediated by the NMDA receptor complex. Alternatively, the compound antagonizes neuronal damage mediated by the voltage-dependent calcium channel. Other useful compounds are those which limit release of glutamate from cells or reduce the intracellular neurotoxic

consequences of glutamate interaction with cell membrane glutamate receptors. Preferably, the compound crosses the blood-retinal barrier.

Particularly preferred compounds are antagonists of the NMDA receptor-channel complex. The term "NMDA receptor antagonists" includes several sub-types of NMDA antagonists including: a) channel blockers--i.e., antagonists that operate uncompetitively to block the NMDA receptor channel; b) receptor antagonists--antagonists that compete with NMDA to act at the NMDA binding site; c) agents acting at either the glycine co-agonist site or any of several modulation sites such as the zinc site, the magnesium site, the redox modulatory site, or the polyamine site; d) agents which inhibit the downstream effects of NMDA receptor stimulation, such as agents that inhibit activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism.

Other compounds that are useful in the invention include voltage-dependent calcium channel antagonists, e.g. those which exert a substantial direct effect on glutamate toxicity mediated by the L-type voltage dependent Ca.sup.++ channel in that they produce a statistically significant result in experiments measuring glutamate induced effects by the general method described in Karschian and Lipton, J. Physiol.418:379-396 (1989) or by other techniques for measuring antagonism of the L-type Ca.sup.++ channel known to those in the art. (We contrast the direct effect so measured with the secondary effects of excitoxicity mediated by other channels, which in turn causes flow through the voltage dependent Ca.sup.++ channels.) Particular candidate compounds include Class I voltage dependent Ca.sup.++ channel antagonists, e.g., phenylalkylamines.

Preferably, the compounds used cross the blood-retina barrier and can be administered chronically. Other useful agents act as antagonists of non-NMDA receptors (glutamate receptor types other than the NMDA receptor complex discussed above), and include agents which block inotropic glutamate receptors

or interact with metabotropic glutamate receptors (Nakanishi, supra). Still other agents act to limit (reduce) release of glutamate from cells, thereby acting upstream from the glutamate receptors in the excitatory neurotoxicity process. Still other agents may act by blocking downstream effects of glutamate receptor stimulation, e.g., the intracellular consequences of glutamate interaction with a cell membrane glutamate receptor, such as agents (like dantrolene) that block the rise in intracellular calcium following stimulation of membrane glutamate receptors.

The most preferred compounds are those capable of crossing the blood-retinal barrier; these compounds may be administered orally, intravenously, or topically and cross intervening barriers including the blood-retina barrier to reach the retinal ganglion cells. Compounds that do not freely cross the blood-retina barrier are less preferred; these compounds may be administered intravitreally to the retina. In the case of compounds that have an intermediate ability to cross the blood-retina barrier, the mode of administration will depend on the dosage required and other factors.

Among the preferred compounds are amantadine derivatives (e.g., memantine, amantadine, and rimantadine), nitroglycerin, dextorphan, dextromethorphan, and CGS-19755. See generally, the compounds listed in Table 2.

The invention is useful for the reduction or prevention (including prophylactic treatment) of damage as a result of proliferative vitreoretinopathy.

In view of our discovery that glutamate is associated with proliferative vitreoretinopathy, the invention features antagonists having certain specific characteristics: the ability to cross the blood-retina barrier; and the ability to be administered chronically. Within those guidelines, any suitable antagonist of the glutamate induced excitotoxicity may be used in accordance with the invention. As mentioned, in preferred embodiments, N-methyl-D-aspartate (NMDA) subtype of glutamate receptor-channel complex may be used to reduce or prevent proliferative vitreoretinopathy-related injury. Many antagonists of the

NMDA receptor have been identified (Watkins et al., Trends in Pharmacological Sci. 11:25, 1990, hereby incorporated by reference). There are several recognized sub-types of NMDA receptor including: a) channel blockers--i.e., antagonists that operate non-competitively to block the NMDA receptor channel; b) receptor antagonists--antagonists that compete with NMDA, acting at the NMDA binding site; c) agents acting at either the glycine co-agonist site or any of several modulation sites such as the zinc site, the magnesium site, the redox modulatory site, or the polyamine site; d) agents which inhibit the downstream effects of NMDA receptor stimulation such as agents that inhibit activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism.

Other compounds that are useful in this invention include non-NMDA receptor antagonists, such as agents which block other types of inotropic glutamate receptors or interact with metabotropic glutamate receptors; voltage-dependent calcium channel antagonists (against L, N, T, and P type channels) (Bean, B. P. Annu. Rev. Physiol. 51:367-384 (1989); Hess, P. Annu. Rev. Neurosci. 13:337-356 (1990)), and are described in greater detail below; and agents which act to decrease the release of glutamate, thereby acting upstream in the excitatory neurotoxicity process.

Table 1, below, lists various suitable NMDA and non-NMDA receptors which do not operate via the voltage-dependent Ca.sup.++ ion channel. Tables 2-4 list antagonists of the voltage dependent Ca.sup.++ channel, which can be used by themselves in connection with the first aspect of the invention, and which can also be used in combination with other antagonists in the second aspect of the invention.

NMDA Antagonists	NMDA Antagonists	NMDA Antagonists
1. Competitive NMDA Antagonists (act at agonist binding site)	2. Channel Blockers (Un-Competitive NMDA Antagonists)	3. Antagonists at Glycine Site of the NMDA Receptor
CGS-19755	MK-801	Kyourenate, 7-

		(CIBA-GEIGY) and other piperdine derivatives, D-2-amino-5-phospho-valerate, D-2-amino-7-phosphonohep-tanoate (AP7)	(Dizocilpine) and other derivatives of dibenzy-ocycloheptene (Merck)	chloro-kyourenate, 5,7-chloro-kyourenate, thio-derivatives, and other derivatives. (Merck)
		CPP {[3-(2-carboxy-	Sigma receptor ligands, e.g.	Indole-2-carboxylic
acid				
		piperazin-4-y-propyl-1-phos-phonic acid]}	Dextrorphan, dextro-methorphan and morphinan derivatives (Hoffman La Roche) such as cara-miphen and timeazole (which also block calcium channels)	
		LY27614, CGP39551, CGP37849, LY233053, LY233536	Ketamine, Tiletamine and other cyclo-hexanes	DNQX
		O-phospho-bornoserine	Phencyclidine (PCP) and derivatives, and pyrazine	Quinoxaline or oxidiazole derivatives including
CNQX,			compounds	NMQX

	MDL100,453	Memantine,	Glycine
partial			
		amantadine,	agonist (e.g.
		rimanta-	Hoecht-Roussel
		dine and	P-9939)
		derivatives	
		CNS 1102 (and	
		related bi- and	
		tri- substituted	
		guanidines)	
		Diamines	
		Conantokan	
		peptide from	
		Cocus	
		geographus	
		Agatoxin-489	
4.	Polyamine Site	5. Redox Site of	6. Other Non-
	of NMDA	NMDA	Competitive
	Receptor	Receptor	NMDA
			Antagonists
	Arcaine and	Oxidized and	Hoechst
	related biguani-	reduced	831917189
	dines and	glutathione	
	biogenic		
	polyamines		
	Ifenprodil and	PQQ (pyrrolo-	SKB
Carvedilol			
	related drugs	quinoline)	
	Diethylene-	Compounds	
	triamine SL	that generate	
	82.0715	Nitric Oxide	
		(NO) or	
		other oxi-	
		dation states	
		of nitrogen	
		monoxide	
		(NO+, NO-)	
		including those	
		listed in the	

		box below
	1,10-diamino-decane (and related inverse agonists)	Nitroglycerin and derivative, Sodium Nitro-prusside, and other NO generating listed on p. 5 of this table
		Nitric oxide sythase (NOS) Inhibitors: Arginine analogs including N-mono-methyl-L-argine (NMA): N-amino-L-arginine (NAA); N-nitro-L-(NNA); N-nitro-L-arginine methyl ester; N-imino-ethyl-L-ornithine
		Flavin Inhibitors: diphenyl-iodinium;
		Calmodulin inhibitors, trifluoperizine
		Calcineurin Inhibitors, e.g., FK-506

			(inhibits calcineurin and thus NOS diphos-phorylase)	
	Inhibitors of Downstream Effects of NMDA		Inhibitors of Downstream Effects of NMDA	Non-NMDA Receptor Antagonists
	7. Agents to inhibit protein kinase C activation by NMDA stimu-lation (involved in NMDA toxicity)	8.	Downstream effects from Receptor Activation	9A. Non-NMDA antagonists (Competitive)
	MDL 27.266 (Merrill Dow) and triazole-one derivatives	8a.	To decrease phopshati-dylinositol metabolism	CNQX, NBQX, YM900, DNQX, PD 140532
	Monosialo-gangliosides (eg GM1 of Fidia Corp.)		kappa opioid receptor agonist: U50488	AMOA (2-amino-3[3-9carboxy-methoxyl-5-
methoxylisox-	and other gang-lioside derivatives		(Upjohn) and dynorphan	azol-4-yl] propionate)
	LIGA20, LIGA4 (may also effect calcium extrusion via calcium ATPase)			
			kappa opioid receptor agonist:	2-phospho-phonoethyl phenylalamine

			PD117302, i.e. methyl, trifluoromethyl	derivatives, 5-ethyl, 5-
			CI-977	5-
		8b.	To decrease hydrogen peroxide and free radical injury, eg antioxidants	
			21-aminosteroid (lazaroids) such as U74500A, U75412E and U74006F	9B. Non-NMDA Non
	competitive		U74389F, FLE26749, Trolex (water soluble alpha tocophenol), 3,5-dialkoxy-4-hydroxy-benzylamines	antagonists GYK152466
			Compounds that generate Nitric Oxide (NO) or other oxidation states of nitrogen monoxide (NO+, NO-) including those listed in	Evans Blue

			the box below
			Nitroglycerin and derivatives,
			Sodium Nitro-prusside, and other NO generating listed on p. 5 of this table
			Nitric oxide synthase (NOS) Inhibitors: Arginine analogs in-cluding N-mono-methyl-L-arginine (NMA); N-amino-L-arginine (NAA); N-nitro-L-arginine (NNA); N-nitro-L-arginine methyl ester, N-iminoethyl-L-ornithine
Agents Active at Metabotropic Glutamate Receptors		Decrease glutamate release	Drugs to decrease intracellular calcium following glutamate receptor stimulation
10a.	Blockers of Metabotropic Glutamate	11.	Agents to decrease glutamate
			12a. Agents to decrease intracellular

	Receptors	release	calcium release
	AP3 (2-amino-3-phosphono-prionic acid)	Adenosine, and derivatives, e.g. cyclo-hexyladenosine	Dantrolene (sodium dantrium); Ryanodine (or ryanodine + caffiene)
10b.			
Agonists of Metabotropic Glutamate Receptors	CNS1145	12b. Agents inhibiting intracellular Calcium-ATPase	
(1S,3R)-1-Amino-cyclo-pentane-1,3-dicarboxylic acid [(1S,3R)-1,4-ACPD], commonly ref as `trans`-ACPD		Conopeptides: SNX-111, SNX-183, SNX-230	Thapsigargin, cyclopiazonic acid, BHQ ([2,5-di-(tert butyl)-benzohydro-quinone; 2,5-di-(tert butyl)-1,4 benzohydro-quinone])
		Omega-Age-IVA, toxin from venom of funnel web spider	
		Compounds that generate Nitric Oxide (NO) or other oxidation states of nitrogen	

monoxide (NO+, NO-) including those listed in the box below
Nitroglycerin and derivatives,
Sodium Nitro-prusside, and other NO generating listed on p. 5 of this table
Nitric oxide synthase (NOS) Inhibitors: Arginine analogs including N-mono-methyl-L-arginine (NMA);
N-amino-L-arginine (NAA)
N-nitro-L-arginine (NNA);
N-nitro-L-arginine methyl ester;
N-iminoethyl-L-ornithine
Additional NO-generating compounds
Isosorbide dinitrate

	(isordil)
	S-nitrosocapto-
	pril (SnoCap)
	Serum albumin
5	coupled to
	nitric oxide
	(SA-NO)
	Cathepsin
	coupled to
10	nitric oxide
	(cathepsin-NO)
	Tissue
	plasminogen
	activator
15	coupled to
	NO (TPA-NO)
	SIN-1 (also
	known as SIN1
	or molsi-
20	domine)
	Ion-nitrosyl
	complexes
	(e.g.,
	nitrosyl-iron
25	complexes,
	with iron in the
	Fe2+ state)
	Nicorandil

30

TABLE 2

Antagonists of the Voltage Dependent Calcium Channels
(N, L, T, P and other types)

	dihydropyridines
35	(e.g., nimodipine)
	phenylalkylamines
	(e.g., verapamil, (S)-emopamil, D-600, D-888)
	benzothiazepines
	(e.g., diltiazem and others)

bepridil and related drugs
diphenylbutylpiperdines
diphenylpiperazines
(e.g., flunarizine/cinnarizine series)
HOE 166 and related drugs
fluspirilene and related drugs
toxins and natural compounds
(e.g., snail toxins -
.omega.conotoxin GVIA and GVIIA, maitotoxin,
taicatoxin, tetrandine, hololena toxin, plectreurys
toxin, funnel-web spider venom and its toxin fraction,
agatoxins including .omega.-agatoxin IIIA and .omega.-agatoxin IVA.

TABLE 2

Antagonists of the Voltage Dependent Calcium Channels
(N, L, T, P and other types)

dihydropyridines
(e.g., nimodipine)
phenylalkylamines
(e.g., verapamil, (S)-emopamil, D-600, D-888)
benzothiazepines
(e.g., diltiazem and others)
bepridil and related drugs
diphenylbutylpiperdines
diphenylpiperazines
(e.g., flunarizine/cinnarizine series)
HOE 166 and related drugs
fluspirilene and related drugs
toxins and natural compounds
(e.g., snail toxins -
.omega.conotoxin GVIA and GVIIA, maitotoxin,
taicatoxin, tetrandine, hololena toxin, plectreurys
toxin, funnel-web spider venom and its toxin fraction,
agatoxins including .omega.-agatoxin IIIA and .omega.-agatoxin IVA.

TABLE 4

OTHER CALCIUM CHANNEL ANTAGONISTS

diclofurime	D-600
pimozide	D-888
prenylamine	Smith Kline 9512
fendiline	ranolzine
perhexiline	lidoflazine
mioflazine	CERM-11956
flunarizine/	R-58735
cinnarizine series	R-56865
verapamil	amiloride
dilfiazine	phenytoin
dipropervine	thioridazine
(S)-emopamil	tricyclic antidepressents

In Vitro Assay

An antagonist may be tested for utility in the method of the invention by monitoring its effect on proliferative retinopathy as follows.

Cultured fibroblasts will be injected into the vitreous of the rabbit eye. After two weeks, the degree of vitreopathy can be assessed histologically. At the time of the initial insult, the animals will be treated with the compound under consideration.

Such models are well known. A few examples (hereby incorporated by reference) included Kiumura et al. Human Gene Therapy, 7:799-808 (1996); Sakamoto et al., Ophthalmology 102:1417-1421 (1995); Handa et al. Experimental Eye Research 62:689-696 (1996); Berger et al. 37:2318-1325 (1996); de Souza et al. Ophthalmologica 209:212-216 (1995); Nakagawa et al. Ophthalmology & Visual Science 36:2388-2395 (1995); Steinhorst et al. Archive for Clinical & Experimental Ophthalmology 232:347-354 (1994).

Use

An effective receptor antagonist will cause a decrease in proliferative vitreoretinopathy. As described above, the preferred compounds which cross the blood-retinal barriers are preferably administered topically or orally in known, physiologically acceptable vehicles including tablets, liquid excipients and suspensions. Those skilled in the art will appreciate how to formulate acceptable therapeutics.

Antagonists may be compounded into a pharmaceutical preparation, using pharmaceutical compounds well-known in the art; the exact formulation and dosage of the antagonist compound depends upon the route of administration. Generally, the effective daily dose of the antagonists will range from 0.01 to 1000 mg/kg.

Other Embodiments

Other embodiments are within the following claims. In the method of the invention, a useful compound may be administered by any means that allows the compound access to the retina. The compounds useful in the method include antagonists of excitatory amino acid receptors (both NMDA and non-NMDA subtypes) that act to reduce retinal cell migration or proliferation or reduce binding of glutamate to the NMDA receptor. The antagonists can act at a modulatory site or a co-agonist site or by blocking the chain of events initiated by receptor activation.